TOWARDS A NEW BIOCHEMISTRY?[1]

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THE atom consists of a nucleus surrounded by a system of electrons. By sharing one or more electrons, atoms can join to form molecules. In such a molecule, as a rule, every electron belongs to one or two atoms. This is our idea of a single small molecule, and this picture has hitherto unconsciously governed our thinking in biochemistry.

The study of crystals and metals, however, has revealed the existence of a different state of matter. If a great number of atoms is arranged with regularity in close proximity, as for instance, in a crystal lattice, the terms of the single valency electrons may fuse into common bands. The electrons in this band cease to belong to one or two atoms only, and belong to the whole system.

These bands or energy levels are separated from possibly higher levels by forbidden zones. Under ordinary conditions all electrons are within the lowest band. If this lowest band contains the maximum number of electrons ($2n$, if the number of atoms is n), as is the case with insulators, the electrons will be unable to transport energy. If, however, one of these electrons is raised by the absorption of energy to a higher level, and comes to be in what we call an excited state, where it will move and transport its energy freely, it will be impossible to say which is the atom to which the excited electron belongs, and the whole system can be looked upon as activated. By falling back to the lower level the electron will give off its excess energy and perform work in a place more or less distant from that of the absorption of energy. This is the case with certain phosphors, as has been shown lately by N. Riehl.[2] Here, as for instance in ZnS, the electron, raised to a higher level by a collision with an α particle, can travel relatively long distances and will fall back to a lower level, giving up its energy, where it meets a Cu atom, present as an impurity. Thus the absorption and emission of energy will proceed independently at different places.

The problem is whether this state of matter, *i.e.*, common energy levels, exists also in living systems. If it does it can not fail to influence profoundly our biological thinking and open new approaches to research and understanding. Protein molecules are systems built up of a great number of atoms, closely packed with great regularity. So theoretically the possibility exists that within these molecules analogous conditions to those in crystals prevail.

The first indication of the existence of such common energy levels was given by the study of photosynthesis, one of the most fundamental biological processes. Emerson and Arnold[3] found that 2,500 chlorophyl molecules form one functional unit. Warburg and Negelein[4] showed that four quanta are necessary for the reduction of one CO_2 molecule. There are observations to indicate that these four quanta must reach the CO_2 molecule simultaneously. Gaffron and Wohl[5] calculated how many chlorophyl molecules must interact to absorb four quanta simultaneously at the weakest optimal illumination. Their calculation showed that only one thousand molecules are capable of doing this. These observations indicate that the electrons, raised to a higher energy level by the absorbed light, can move and transport their energy freely through the system of chlorophyl molecules.

Kubowitz and Haas[6] have measured the inactivation-spectrum of urease, and P. Jordan[7] has pointed out that their results are in agreement with the idea that common energy levels exist within this protein molecule. At present K. Laki and M. Gerendás are engaged in my laboratory in the study of the inactivation-spectrum of fumarase, crystallized by Laki. Their results also indicate that the energy absorbed may leave the place of its absorption and cause a break of links at a different place, thus traveling at some distance through the molecule.[8]

[1] Korányi Memorial Lecture, given in Budapest on March 21, 1941.

[2] N. Riehl, *Naturwiss.*, 28: 601, 1940.

[3] R. Emerson and W. Arnold, *Jour. gen. Physiol.*, 16: 191, 1930.

[4] O. Warburg and E. Negelein, *Naturwiss.*, 13: 985, 1925.

[5] H. Gaffron and K. Wohl, *Naturwiss.*, 24: 81, 1936.

[6] F. Kubowitz and E. Haas, *Biochem. Zeits.*, 257: 337, 1933.

[7] P. Jordan, *Naturwiss.*, 42: 693, 1938.

The more interesting question, however, is not whether common energy levels exist within one molecule, but whether protein molecules can join into more extended systems with common energy levels. It would be difficult to picture such a continuum built up of globular protein molecules, and protein molecules have hitherto, with rare exceptions, been found to be globular. However, last year Banga and I[9] found that the proteins building up the solid structure of the cell are fibrous, and that these fibrous molecules as shown by their strong thixotropy, are interconnected by intermolecular forces. Chloroplasts also contain fibrous proteins.

This finding allows us to suppose tentatively that a greater number of molecules may join to form such energy continua, along which energy, *viz.,* excited electrons, may travel a certain distance. The study of gene-mutation, introduced by x-rays and ultraviolet light, also indicates such a possibility.

It can not be expected that any single observation will definitely solve this problem. Only the accumulation of a great mass of data will answer these questions. But even at this early stage we are justified in reconsidering the biological problems in the light of these possibilities.

My own biochemical research of two decades has yielded one or another insignificant result—the isolation of this or that—but whenever I was faced with a fundamental problem, I failed. When these problems are reconsidered in the light of common energy levels an easy explanation offers itself. I will enumerate a few of these problems starting with one which arose lately in collaboration with Banga.[9]

The contractile element in muscle is myosine, a protein built up of fibrous molecules. These molecules are arranged in small, primitive bundles. A great number of such primitive bundles forms one microscopic fibril. The energy of muscular contraction is derived from the splitting of adenosine triphosphate. The adenosinetriphosphatase activity is bound up with myosine, but our measurements indicate that only a very small fraction of myosine molecules can be endowed with such activity. The problem is, how the energy liberated by a molecule can be communicated to a great number of similar molecules. The common energy levels give an easy answer.

Another problem that troubled me for many years was why the enzymes involved in oxidation and fermentation can be separated so sharply into soluble and insoluble ones. The enzymes involved in lactic fermentation of muscle are soluble, while the enzymes involved in oxidation are insoluble, *i.e.,* bound to the insoluble fibrous proteins of the cell. This difference can be explained if we suppose that the latter are part of a system with common energy levels. In lactic fermentation no such common levels are necessary, for the single enzymes do not interact but react in series with soluble molecules.

Still another problem, closely connected with the former, is how the enzymes of oxidation interact. In part of the oxidation system electrons wander directly from enzyme to enzyme. The enzymes, being insoluble, have no free molecular motion and must be arranged so that their small reactive groups are at atomic distances. It is possible to arrange two large protein molecules in such a way, but it is geometrically impossible to so arrange a whole series. Even if we could devise such an arrangement, it would still be incomprehensible how the energy liberated by the passing of an electron from one substance to the other, *viz.,* from one Fe atom to the other, could do anything useful. All this can be understood if we suppose that the single catalysts are connected with different, distinct energy levels and that the electrons do not pass directly from one substance to the other but travel within the corresponding energy band, and can fall to a lower level and give off energy only at a place where they can do work (*e.g.,* a synthesis), analogous to the ZnS phosphors of Riehl. If the cell and with it the energy levels are disturbed in some way, we can expect the electrons to fall freely to lower levels at any place. This might explain why catabolic processes prevail over anabolic ones in damaged tissues (and cancer?), why certain oxidations (catechol-oxidase) are activated by damage, why chloroplasts refuse to build up carbohydrates, and why viruses refuse to multiply outside the cell.

In closing, I wish to mention three problems from outside the field of my own work. One of my difficulties with protein chemistry was that I could not imagine how such a protein molecule can "live." Even the most involved protein structural formula looks "stupid," if I may say so. If the atomic structure is only the backbone underlying the common energy levels, the thing becomes more likely. It is equally difficult to understand the great biological activity of certain molecules. R. Kuhn, F. Moewus and D. Jerchel[10] have shown lately that one single crocin molecule is capable of inducing a sexual change in a whole alga. If the cell forms an energy continuum, any substance, approaching at any point, can upset the whole system, making, so to say, a hole in the continuum.

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[8] If common energy levels are present in native protein molecules this can not fail to contribute to the stability of the molecule and influence its immunological behavior.

[9] J. Banga and A. Szent-Györgyi, Science, 92: 514, 1940; *Enzymologia,* 9: 111, 1940.

[10] R. Kuhn, F. Moewus and D. Jerchel, *Ber. d. Chem. Ges.,* 71: 1541, 1938.

Then we do not know what a "cell" really means, or why the kidney, for instance, is subdivided into such units. Possibly the cell wall is the border line of the common energy levels.

Biochemistry is, at present, in a peculiar state. By means of our active substances we can produce the most astounding biological reactions, but we fail wherever a real explanation of molecular mechanisms is wanted. It looks as if some basic fact about life were still missing, without which any real understanding is impossible. It may be that the knowledge of common energy levels will start a new period in biochemistry, taking this science into the realm of quantum-mechanics.